Clinical Development

TBM100C / Tobramycin Inhalation Powder

CTBM100C2419

A multicenter, human factors validation study in cystic fibrosis patients aged 6 years and older to evaluate the user interface of TOBI® Podhaler™ (tobramycin inhalation powder) using placebo capsules

Statistical Analysis Plan (SAP)

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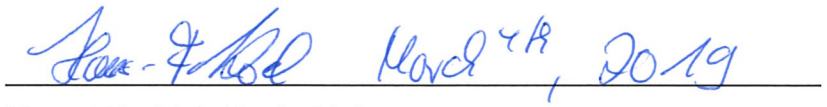
Approved by:  March 4th, 2019

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Document type: SAP Documentation

Document status: Final 2.0

Release date: 04-Mar-2019
Number of pages: 8

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
21-Jun-2018	*Prior to DB lock*	*Creation of final version*	*N/A - First version*	*NA*
04-Mar-2019	*Prior to DB lock*	*Sponsor change*	*Novartis replaced by Mylan or name of CRO* *Note added that summary tables are only provided if at least five patients report any AE*	*Title page, header, sections 1 & 2* *Section 2.5.1*

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
CF	Cystic Fibrosis
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
HF	Human Factors
MedDRA	Medical Dictionary for Drug Regulatory Activities
PMR	Post-marketing Requirement
PT	Preferred Term
RAP	Report and Analysis Process
REALM-SF	Rapid Estimate of Adult Literacy in Medicine-Short Form
SAE	Serious Adverse Event
SAF	Safety Set
SF	Screen Failure Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
US	United States
WHO	World Health Organization

1 Introduction

This study is a human factors validation study to validate the user interface of TOBI Podhaler by establishing that the product can support safe and effective use for the intended users.

The study is being conducted to fulfill US FDA post-marketing requirement (PMR) 1928-5:

Conduct a human factors validation study to demonstrate that the user interface of the product can support safe and effective use for the intended users. The human factors validation study should be conducted in patients aged 6 years and older under simulated yet representative of realistic use conditions and include all the critical tasks identified from your updated use-related risk analysis.

In addition to Human Factor (HF) assessments, limited clinical data (e.g., patient demographics, AEs, SAEs, vital signs, medical history and concomitant medications) will be collected.

NOTE: this document describes the summaries on clinical safety data only, i.e., the data collected on Mylan eCRFs. The HF data will not be entered into Mylan database and HF analysis is out of scope of this document.

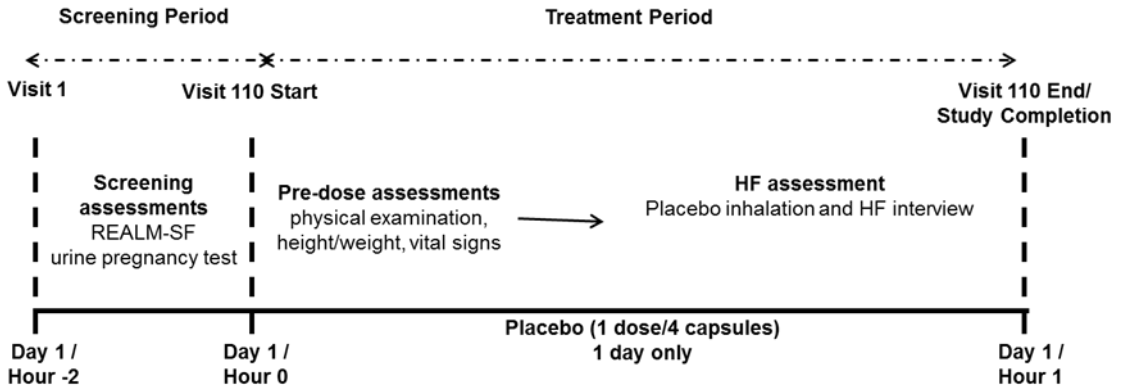
1.1 Study design

This is an open-label, non-randomized, single placebo arm, single visit HF study.

The study will enroll 50 cystic fibrosis (CF) subjects with the aim of having 45 subjects completing the study across three age groups of approximately 15 subjects each (6-10 years, 11-17 years, and ≥ 18 years). Only CF patients who are naïve to the use of the Podhaler device will be enrolled. Patients will take a four-capsule dose from the Podhaler device using placebo capsules (powder-filled) at the visit. The study requires that any caregiver is also naïve to the use of the Podhaler device.

These patients and caregivers will not be trained prior to using TOBI Podhaler and will be observed during the dosing procedure and interviewed afterwards to establish root cause of any errors during the inhalation process.

Figure 1-1 Study design



1.2 Study objectives and endpoints

The objective of this study is to evaluate whether the user interface of TOBI Podhaler can support safe and effective use for patients with CF by assessing use errors and close calls associated with the simulated inhalation of one dose (4 capsules) using the TOBI Podhaler device. HF assessments will be performed to primarily support the objective; data collection, analyses and reports on HF data will be done independently by Team Consulting, a contract research organization (CRO), and are not discussed in this document.

2 Statistical methods

The clinical data as collected on eCRFs will be reported as the supplementary information in the study report. This will be performed by ICON using SAS© 9.4.

Because there is only one placebo arm (and one-dose), no comparison or statistical hypothesis test is applicable to this study. All data will be summarized descriptively based on data collected in clinical database. More details will be defined in a separate document with mocked shells.

2.1 Data analysis general information

In general, categorical variables will be presented as the number and percentage of subjects in each category. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum). The analysis will be based the safety set (patients who have inhaled the contents of at least one capsule of placebo).

2.2 Analysis sets

Two analysis sets are defined in the protocol:

The Screen Failure Set (SF) includes all patients who signed the informed consent and failed the screening.

The Safety set (SAF) includes all patients who entered the study and who have inhaled the contents of at least one capsule of placebo, regardless of whether the related HF assessment is completed.

NOTE: SAF set will be used for all analyses discussed in this document.

2.2.1 Subgroup of interest

Three age subgroups (6-10 years, 11-17 years, and ≥ 18 years) will be separately presented in additional to overall summaries. This will apply to all post-text tables and listings that will be defined in the mock shells document.

2.3 Patient disposition, demographics and other baseline characteristics

Descriptive statistics for demographics (age, sex, race and ethnicity), baseline characteristics (height, body weight, systolic and diastolic blood pressure, radial pulse rate, respiratory rate, and body temperature), and summaries of relevant disease history/current medical condition including CF signs and symptoms will be presented for SAF set overall and by age subgroup.

Number of patients included in each analysis set (SF and SAF) will be reported, as well as reasons for screen failures. Patient dispositions (number of patients who completed/discontinued the study with discontinuation reasons) and protocol deviations will be reported for safety set.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Treatment (placebo) compliance is part of HF assessments and will be summarized in the HF report.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) terminology.

Standard summary tables of concomitant medications by ATC class and non-drug therapies will be provided.

2.5 Safety analyses

2.5.1 Adverse events (AEs)

Adverse events and SAEs will be coded according to the MedDRA coding system using the latest version at the time of generating the report.

AEs and SAEs will be summarized by system organ class (SOC) and preferred term (PT) for the safety set overall and by age subgroups. The same event, as defined by preferred term, will be counted only once for each subject.

The maximum AE severity and AEs resulting in withdrawal of treatment will also be summarized by SOC and preferred term.

Note: Summary tables will only be provided if at least five patients report any AE.

In additional to the tabulations, listings will be provided for AEs and SAEs.

2.5.2 Deaths

Deaths if any occurred will be reported by a listing including all relevant information as collected on SAE eCRF pages.

2.5.3 Laboratory data

Not applicable.

2.5.4 Other safety data

2.5.4.1 Vital signs

Vital signs, including systolic and diastolic blood pressure, radial pulse rate, respiratory rate, and body temperature will be measured only once in the trial and will be summarized along with other baseline parameters (Section 2.3).

3 Sample size calculation

The FDA guidance document 'Applying Human Factors and Usability Engineering to Medical Devices' (FDA 2016) suggests a minimum of 15 subjects per distinct user group is required for validation testing. Per the guidance, "The FDA views populations as distinct when their abilities or the nature of their device interactions are expected to be different". In the case of CF, age is the only characteristic which is likely to contribute to variation in abilities and/or device interaction. Therefore, the study will include 45 subjects with approximately 15 subjects in each of the three age groups (6-10 years, 11-17 years, and ≥ 18 years).

4 Change to protocol specified analyses

None

5 References

US Department of Health and Human Services, Public Health Service, Food and Drug Administration (2016) Applying Human Factors and Usability Engineering to Medical Devices